Conclusion: Oral BYK408740 at 600 mg QD continuously d1−5 in a 14 day cycle is well-tolerated. BYK408740 shows a favourable PK profile, with high bioavailability and low inter-pt variability. The modulation of plasma biomarkers further indicates drug activity. Dose escalation on this schedule continues.

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Final results of a Phase I study of cediranib, a VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors

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Background: Cediranib (AZD2171) is a highly potent and selective inhibitor of vascular endothelial growth factor (VEGF) signaling. The purpose of this Phase I study was to evaluate the safety and tolerability of increasing doses of cediranib in Japanese patients (pts), with additional assessments of pharmacokinetics (PK) and efficacy.
Methods: In the dose-ascending phase (part A), pts with advanced solid tumors refractory to standard therapies received once-daily oral cediranib (10−45 mg). Doses were escalated in successive cohorts until the maximum tolerated dose (MTD) was identified. In the expanded-cohort phase (part B), 24 pts with non-small-cell lung cancer (NSCLC) and colorectal cancer (CRC) received cediranib at the MTD.
Results: Between Oct 2005 and March 2007 a total of 40 pts (mean age: 55 [26−73], male/female: 24/16, PS 0/1: 13/27) were recruited. In part A, 16 pts with NSCLC (5), CRC (4) or other tumor types (7) received cediranib 10 (3), 20 (3), 30 (3) or 45 (7) mg/day. Since 3/6 evaluable pts receiving 45 mg/day experienced DLTs (proteinuria, proteinuria + diarrhea, and thrombocytopenia), cediranib 30 mg/day was defined as the MTD for further investigation in part B. Following a single dose of cediranib 10−45 mg, the maximum plasma concentration was achieved 2−4 hours post dosing and the mean terminal half-life ranged from 19−28 hours. At 20 mg/day, the unbound minimum plasma concentration was 3.85 times the human umbilical vein endothelial cell proliferation IC50. Overall common adverse events (AEs) and laboratory abnormalities of CTCAE grade 1−4//3−4 were diarrhea (85/10%), hypertension (80/0%), hand–foot syndrome (68/2.5%), blood erythropoietin increased (73/0%), blood TSH increased (70/0%), and proteinuria (68/10%). Upward tendency in VEGF and reductions in soluble VEGFR-2 were observed in part B. The PK parameters and overall AE profile were similar to those seen in a Western population. Of 32 pts who were eligible for RECIST assessments there were 2 confirmed partial responses (alveolar soft tissue sarcoma and CRC) and 24 pts with stable disease $\geqslant$8 weeks; the disease control rate was 81% (26/32). Six pts in part A have continued with cediranib for more than 1 year.
Conclusions: Once-daily oral cediranib at doses of 30 mg or less was generally well tolerated in this population of Japanese pts with a manageable adverse event profile and was associated with encouraging antitumor activity.

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Phase I study of XL844, a novel Chk1 and Chk2 kinase inhibitor, in combination with gemcitabine in patients with advanced malignancies

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Background: XL844 is a potent inhibitor of the cell cycle checkpoint kinases Chk1 and Chk2, which are implicated in tumor cell resistance to cytotoxic chemotherapy. In vitro clonogenic assays and in vivo mouse xenograft studies have shown that XL844 potentiates the activity of chemotherapeutic agents such as gemcitabine.
Methods: Patients (Pts) with advanced malignancies were enrolled in successive cohorts of a Phase 1 study with an initial 6-week (wk) treatment cycle followed by 4-wk cycles. During the first 5 weeks of the initial cycle, pts received oral XL844 on the first 2 days of each week and received a gemcitabine infusion (800 mg/m^2) 8 hours prior to the first XL844 dose in wks 3−5. Thereafter, pts received the combination in wks 1−3 of subsequent cycles. Tumor response was assessed approximately every 2 cycles. Serial blood samples were collected for plasma pharmacokinetic (PK) assessment.
Results: In this ongoing study, 20 pts have been treated in 4 cohorts at XL844 doses of 0.8, 1.1, 1.6 and 2.35 mg/kg/day. Tumor types included colorectal carcinoma (CRC, 8 pts), ocular melanoma and gastric carcinoma (2 pts each), clear cell carcinoma, rhabdomyosarcoma, mesothelioma, gastroesophageal junction, pancreatic, periampullary, endometrial and small intestinal adenocarcinoma (1 pt each). Five pts achieved stable disease (SD) for $\geqslant$4 months (mo) including 1 pt each with periampullary cancer (9+mo), ocular melanoma (6.5 mo), CRC (5 mo), rhabdomyosarcoma (4.5 mo), and gastric carcinoma (4 mo). Treatment-related adverse events (AEs) included nausea and vomiting (1 pt each). Two DLTs occurred to date: 1 grade 4 thrombocytopenia (Cohort 1), and 1 grade 3 lipase elevation (Cohort 4). The maximum tolerated dose has not yet been reached and dose escalation is ongoing. A preliminary PK analysis for XL844 indicates that mean exposure (C_{max} and AUC) increased proportionally to dose between 0.8 and 1.6 mg/kg. Mean $t_{1/2}$ ranged from 2−4.6 hrs on Day 1 and 4.2–27.9 hrs on Day 2. Minimal accumulation was observed after multiple doses of XL844. No apparent PK interaction between XL844 and gemcitabine was observed.
Conclusions: XL844 was generally well tolerated. Stable disease ($\geqslant$4 mo) was observed in patients with various tumor types. The MTD has not yet been defined and dose escalation continues.

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Effect of oral (PO) casopitant, a novel NK-1 receptor antagonist, on the pharmacokinetics (PK) and safety profile of intravenous (IV) docetaxel

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Background: Casopitant, in combination with a standard pre-medication regimen of a 5HT3 antagonist and dexamethasone (5HT3/Dex), is currently in development for the prevention of chemotherapy-induced nausea and vomiting. Because casopitant is a weak-to-moderate inhibitor of CYP3A4, this study evaluated whether oral casopitant would modify the PK and safety profile of the CYP3A4 substrate, docetaxel, in cancer patients (pts).
Methods: Pts scheduled to receive at least two doses of weekly IV docetaxel (20−40 mg/m^2) were enrolled in a randomized two-period crossover study. They received docetaxel (0 h) and a 5HT3/Dex regimen (8 mg PO ondansetron, −0.5 h and 8 mg PO Dex −12 h, −1 h and +12 h) alone, and the same regimen of docetaxel and 5HT3/Dex in combination with oral casopitant (150 mg PO, −1.0 h). The PK and safety profile of docetaxel was studied.
Results: Twelve pts have been enrolled in the study. Descriptive safety data for 10 pts and a planned interim evaluation of PK data for five evaluable pts who have completed study follow-up are presented herein; data for the remaining pts are currently being analyzed for presentation of final study data for all 12 pts at the meeting. The geometric mean (CV%) AUC for docetaxel treatment without casopitant was 968 (40%) ng.h/mL and for docetaxel co-administered with casopitant was 1080 (31%) ng.h/mL, whereas the Cmax was 819 (43%) ng/mL for docetaxel without casopitant and 866 (26%) ng/mL for docetaxel after co-administration with casopitant. AE profiles were similar in both regimens and only one AE, diarrhea, was considered related to study medication. Two SAEs, severe pseudomonal pneumonia and orbital cellulitis, were not considered related to study medication. There were no differences in absolute neutrophil count or in other hematological values between the two regimens.
Conclusions: Based on interim data, the addition of a single-dose 150 mg oral casopitant to a regimen of single-dose IV docetaxel and 5HT3/Dex does not appear to result in a clinically relevant change in the pharmacokinetic disposition or the safety profile of docetaxel.